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Interventional cardiology, where real life and science do not necessarily meet†

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Evidence-based diagnosis, decision-making, and therapy appear a must these days. Generating and publishing evidence is a tedious job according to ever new and tightened research practice regulations. Rules will never prevent the typical human behaviour from showing the new thing to be shinier and the old thing dustier than they really are. The medical community is solicited to concoct a meal that is gullible for patients, authorities, and third-party payers out of the available evidence (after applying some conversion factors correcting the common bias of the researchers), anticipation of what will be the evidence tomorrow, common sense, and digested experience. Examples of misguidance by poorly produced or misinterpreted evidence are plentiful in interventional cardiology as they are in other disciplines. Coronary stents, for instance, were first underestimated due to the fact that they were generally used in bailout situations where the outcome remained rather dismal in spite of the salvaging potential of stents. Then they were overused quite uncritically rather to the detriment of the patient. Now with the high quality of the modern drug-eluting stents (DESs), the overuse persists but is no longer a concern. However, the enhanced potential of DESs compared with bare-metal stents was poorly exploited for >10 years because of reports that slipped through the meshes of good review and publication practice to convey the untenable message that bare-metal stents were preferable in many situations. As other examples, use of the fractional flow reserve (FFR) for decision-making has to be questioned despite prominently published reports recommending it. Fixing a lesion is today easier and hardly more complication prone than assessing it with the FFR. Closure of the patent foramen ovale may never be properly applied, because the collection of the understandably requested evidence takes decades, a follow-up duration that makes research unattractive to physicians and financiers. Transarterial aortic valve replacement, finally, is certain to eventually supplant surgical aortic valve replacement. However, this should have already been accomplished as a logical progress. The adoption of this remarkable breakthrough technology is slowed down by the quest for providing randomized evidence in patients, for whom the evidence should rather be derived from already existing studies, and by the quest to triage all these patients in a heart team, meaning to also keep the surgeons happy, although these patients do not really need them.

Keywords Interventional cardiology • Coronary angioplasty • Scientific rigour • Publication bias • Coronary stenting

Introduction

When interpreting scientific data, in particular in medicine, there is a conversion factor to be imputed. It is normal human behaviour and ubiquitously accepted to be biased for the new thing or technique reported in a scientific paper. Hence, a comparative study, randomized or not, will show the old and conventional comparator worse than it really is and the new thing better. Applying this conversion factor to a study showing a small albeit significant advantage of the new thing invalidates the claimed significance and perhaps even annihilates the numerical advantage. A study showing equipoise converts into one with inferiority of the new thing, perhaps even to a significant degree. Only the presence of an apparently huge advantage of the new thing guarantees a real progress. Yet, again the conversion factor needs to be applied and may well unveil this advantage as a rather modest one.

Carrying that thought through, evidence-based medicine, an uncontestedly laudable product of the last century, loses a number of realms that are currently considered to be checked off and carved into stone. Personal interpretation of data and experience must fill the gaps that were once thought to be closed but are now reopened. And this is not necessarily a bad thing. Collecting evidence in a randomized fashion, ideally with double-blind, double-dummy, and sham-controlled design, could well be overrated. Currently, it is a declared holy grail but that may take bizarre shapes. The rigour of the leading scientific journals, in particular in medicine where nothing less than survival is at stake, is meant to protect against hype and fraud. On the other hand, it may also produce conclusions

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and recommendations ridiculed by common sense. For instance, pharmaceutical companies like to include large numbers of participants in randomized trials. This practice has two main reasons that justify the costs. First, a large trial is more likely to show a small advantage of the new drug as a significant one. Second, broad inclusion criteria yield a large target population once a benefit is shown.

As a fictitious example, reading glass producers would have a great interest in a trial randomizing the entire world population into two halves. One half would read the newspaper with reading glasses and the other half without. Beyond doubt, a significant advantage of using reading glasses would be proved. The conclusion in the scientific report would be: according to this positive trial on all comers, newspapers should only be read with reading glasses. The market for reading glasses would expand from people >40 years (the segment that the study should have been limited to) to everybody.

Even more grotesquely misleading conclusions can emanate from poorly conceived or sloppily conducted randomized trials. Current publication criteria for randomized trials do not allow one to alter the endpoint of a study after the study has commenced. Neither do they allow one to hypothesize in the abstract or the final conclusions of the paper on how the results might have been if the design or endpoints of the study had been chosen differently.

Again fictitious but nonetheless exemplary, 20 people are put on a plane to find out if it is advantageous to wear a parachute when jumping off the plane. The analysis of the state of the jumpers had been fixed and hence published at 1 min after leaving the plane, ignoring the fact that jumping off at 5000 m nobody will have reached the ground at 1 min. The study will show no benefit of wearing a parachute. In contrast, there will be a slight disadvantage if, for instance, in the group with parachutes one person suffers a scratch on the cheek sliding into the shoulder straps of the parachute and one squeezes a thumb closing a buckle of the parachute. While this would not suffice to recommend against the use of a parachute, the only acceptable conclusion in a top journal would be: The study showed no advantage of wearing a parachute when jumping off a plane. The very example can be used to lead the intention-to-treat dogma ad absurdum. Imagine the same study with a properly timed endpoint but a mix-up of groups published as an intention-to-treat analysis only.

Misleading data in interventional cardiology

Coronary stents

When coronary stents were introduced into clinical medicine,[1,2] they were initially blamed for poor results for all the wrong reasons. In contrast to the other so-called new devices of the 1980s, laser therapy and atherectomy, stents were initially exclusively used for bailout situations, i.e. poor results or abrupt closures after plain old balloon angioplasty (POBA). Consequently, the results remained fraught with high myocardial infarction and death rates despite the clear-cut potential of stents to avoid just those. The other so-called new devices were typically used electively in selected patients. They yielded results that were actually not competitive with POBA but appeared superior to the stent results obtained in patients already in a dire situation at the start of stenting.[3,4] On the other hand, it was already established as a fact that ~70% of lesions yielded a result after POBA that was clinically perfect (no abrupt or late closure and no significant restenosis) and could therefore not possibly be improved by a stent. In the pre-stent era, clinically relevant vessel closures occurred in ~5% and restenoses creating symptoms or needing re-interventions in ~25%. From the 30% potential candidate lesions for a better result with the use of a coronary stent, one would logically have to deduce ~5% of lesions with a negative outcome in spite or because of stenting. This entails the impossibility to implant a stent in ~2%, acute or late stent thrombosis in ~2%, and a worse type of restenosis than expected without a stent in ~1%. Simple math indicates that only 25% of lesions attempted by percutaneous coronary intervention (PCI) could possibly benefit from the implantation of a coronary stent. Stenting in 100% makes sure that these 25% of lesions are included. However, it unnecessarily imposes the risks of a stent to the 75% of patients in whom a stent benefit to counterbalance the stent risks is theoretically excluded. Trying to implant a stent only in the 25% of lesions potentially benefitting from it entails even in the most experienced hands that lesions would be misclassified and some of those possibly benefitting from a stent would not get it. So, while the coronary stents were still far from perfect, a coronary stenting rate of ~50% of lesions would probably have been ideal. A publication showed a mortality rate in stented patients of 6 vs. 3% in POBA patients at 6 years in one of the initial trials randomizing stenting against POBA.[5] This was driven by a myocardial infarction rate of 8 vs. 4%, respectively. This study imposed conditional rather than universal stenting but it was scotomized. Moreover, meta-analysing the randomized trials comparing POBA with coronary stents, it was quite conspicuously demonstrated in about 10 000 patients, when focusing on the potential of coronary stents to prevent repeat PCI, that the maximum benefit of coronary stenting was already attained with a stenting rate of 20–40%.[6] That publication was equally ignored, the era of default stenting having already been ushered in. Moreover, the fairly small need for repeat PCI at ~5% with a stenting rate of 20% or more with a bare-metal stent (BMS) in that publication created a difficult background for showing a significant reduction in re-interventions with the drug-eluting stent (DES) about to be clinically introduced in 2003 when the paper was published. *Figure 1* nicely illustrates how the uncontested advantage in terms of a reduced need for re-intervention of DESs over the initial BMSs was amplified in a scientifically questionable but purposeful way, in that case beneficial for patients.[7–11]

While DESs got more praise than they deserved in the beginning, they undeservedly fell on the dark side of popularity in the so-called DES fire storm in 2006[12] (*Figure 2*[13]). Focusing on the increased risk for stent thrombosis during a narrow time window after the first year, when the initial DESs were more prone to fissures in the thin stent coat with endothelium than the BMSs, led to the fact that the well-deserved upsurge of the DES was not only halted but reversed. It took over 10 years to realize that this isolated depiction of a problem, that would have been but a small concern if it had been shown in full context, was a false reason to reserve DESs for selected patients while all patients should have received them. Nowadays, it is acknowledged that DESs have a reduced overall thrombosis risk in particular because of their low initial risk for stent

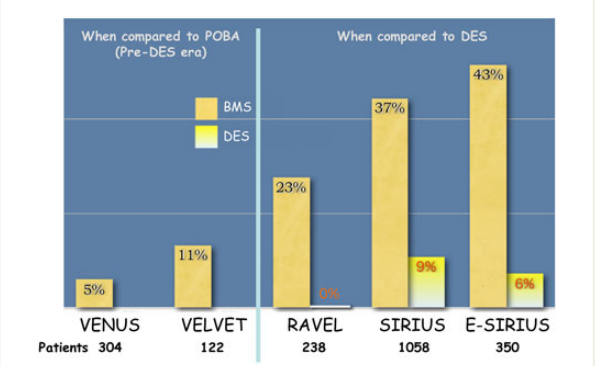

Figure 1 Restenosis rates of the Bx-Velocity stent, a bare-metal stent, and its sibling the Cypher stent, a drug-eluting stent. The left panel shows the restenosis rates of the bare-metal stent examined when bare-metal stent was the good guy (new thing) compared with plain old balloon angioplasty in the VENUS[7] and the VELVET[8] trials. They were much lower than those in the RAVEL,[9] the SIRIUS,[10] and the E-SIRIUS[11] randomized trials with exactly the same bare-metal stent and comparable patients. This time the bare-metal stent was the bad guy (old thing) used to highlight the virtues of the modification of this bare-metal stent to an active drug-eluting stent. Had the restenosis rates of the drug-eluting stent been presented on the background of the restenosis rates of the bare-metal stent as depicted while it benefited from the fact that bare-metal stent was the new thing compared with plain old balloon angioplasty (left side, plain old balloon angioplasty results not displayed), its advantage would have been difficult to discern. The common mechanism to make the old comparator look worse and the new thing better than in reality is what was conveyed and consequently retained from these seminal trials introducing the drug-eluting stent.

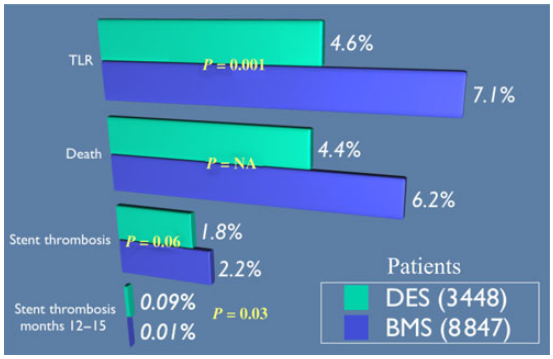

Figure 2 Distorted view of the stent thrombosis risk of early drug-eluting stents. Pointing exclusively to the bottom panel with the significantly increased risk for stent thrombosis during months 12–15 of follow-up with drug-eluting stents or bare-metal stents in an all-comers cohort of patients undergoing coronary stenting, without putting it into relation of all events during the entire follow-up period, put drug-eluting stents into ill-deserved disrepute. Not only the drastically reduced need for target lesion revascularization but also decreased (albeit not to a significant extent) rates of overall death and overall stent thrombosis more than compensated for the blemish after the first year, reported blown out of proportion.

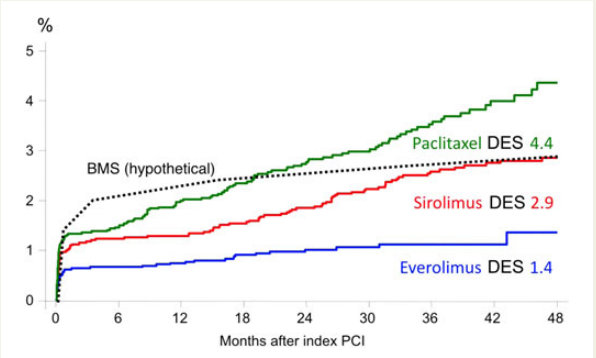

Figure 3 Stent thrombosis rates during follow-up after percutaneous coronary intervention of first-generation drug-eluting stents with paclitaxel or sirolimus and a current drug-eluting stent with everolimus. A typical bare-metal stent thrombosis risk is added for reference.

thrombosis. While this initial benefit of DESs was caught up in part by late stent thrombosis with the early generations of DESs, this is no longer the case. Current DESs are safer throughout all follow-up periods. And this was always independent of the antiplatelet regimen as it was also apparent in randomized trials with identical follow-up drug schemes. While people prone to stent thrombosis (e.g. not able to tolerate antiplatelets or required to discontinue them for surgery) should have received a DES rather than a BMS all along, they typically received a BMS for the good part of a decade based on this misinterpretation of facts secondary to a number of skewed reports on the matter ~10 years ago. For instance, in patients with renal dialysis the use of DESs dropped from almost 90% to ~50% in the USA. The adoption of 100% DES use in these patients, justified on the basis of the now documented improved outcome over that with BMSs including a significant survival benefit[14], was inappropriately delayed. *Figure 3*[15] depicts stent thrombosis rates with various stents. *Figure 4* explains the propensity for stent thrombosis or restenosis of the various stent designs.

Fractional flow reserve

While the assessment of the fractional flow reserve (FFR) to determine the haemodynamic significance of a coronary stenosis has been around as a valid but largely ignored research tool for more than a decade,[16] it turned heads when papers were published that appeared to prove a clinical benefit of using the FFR as a decision tool whether or not to perform PCI.[17–20] Intuitively, it does not make sense to cross a questionably significant coronary stenosis with a guide wire just to perform a fairly complex provocation manoeuvre to determine the current haemodynamic significance in an increased flow situation mimicking physical exercise. In particular, in the realm of easy to implant and utterly safe DESs, fixing the lesion is faster and about as safe as assessing it with the FFR. If the lesion

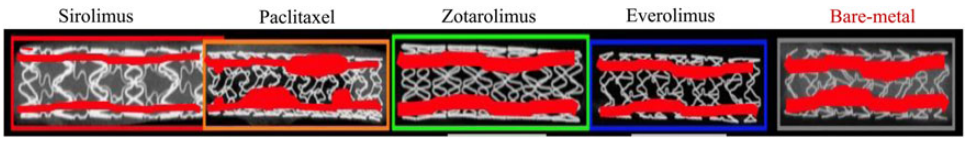

Figure 4 Endothelial coverage of drug-eluting stents with sirolimus, paclitaxel, zotarolimus, or everolimus compared with that of a bare-metal stent. The first-generation drug-eluting stent with sirolimus possessed too thin an endothelial coat, resulting in a low restenosis rate but a significant risk for late thrombosis. The other first-generation drug-eluting stent with paclitaxel had an endothelial coat that was quite thin, particularly on the stent struts themselves, and thereby vulnerable to erosion and stent thrombosis. Yet it also had thicker segments in between the struts, creating a significant degree of restenosis. The newer drug-eluting stents with zotarolimus or everolimus yield a homogeneous endothelial coat, thick enough to prevent erosion and stent thrombosis but still thin enough to result in significantly less restenosis than the bare-metal stent (far right), featuring more lumen loss but a fairly low risk of late erosion and stent thrombosis.

was indeed not yet haemodynamically significant, it most likely would evolve to that point over time and assessing the FFR may just be the reason why, as the FFR wire irritates the endothelium, which can lead to a bout of plaque promotion. Even in the unlikely event that this particular borderline lesion will never mature to a significant one in the patient's life time, having put in a modern DES carries an overall risk of only ~1% to cause an adverse event, anytime. The recently published 5-year follow-up of the FFR vs. angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME) trial[21] claims to justify the use of the FFR for decision-making by the fact that, over 5 years of follow-up, the non-stented lesions that had a normal FFR at the moment of assessment did not cause a significant number of problems. Logic and clinical experience render these findings hard to believe. The fact that, in FAME, the main lesions were stented and only one additional (secondary or tertiary) lesion was randomized to FFR-guided intervention may provide an explanation. Neglecting such an unimportant additional lesion may indeed not carry a palpable disadvantage over 5 years. Neglecting the culprit lesion that brought the patient to the catheterization laboratory must be less favourable than fixing it with a modern DES. In fact this is what the FAME II trial showed albeit without admitting to it (*Figure 5*).[19]

Figure 6 illustrates why PCI might be the better choice over conservative treatment, irrespective of trials stating the opposite.[21,22] There are indeed several reports attesting PCI a survival benefit in patients with stable coronary artery disease.[23–25] They underscore the importance of a long follow-up as coronary artery disease is as much a slow killer as it appears to be a sudden killer,[23] the transient loss of life-saving power of early (drug-eluting) stents,[24] and the fact that 20% of myocardium at risk suffices to render PCI a life saver.[25]

Radial approach for coronary intervention

In the late 1980s, it was proposed to perform coronary angiography[26] and PCI[27] through a puncture of the radial artery. This afforded immediate ambulation and a puncture site that was more easily controllable than a femoral one. An initial enthusiasm was curbed by the technically more challenging radial access and the more intricate path to the coronary arteries. Only a negligible minority of operators continued to use that access on a routine basis[28] until papers appeared stating that the radial access was prognostically superior to the femoral access in patients with acute coronary artery disease.[29,30] These publications are about to enforce a change of paradigm[31] which may not necessarily be in the interest of patients. Intuitively acute coronary syndromes, particularly large ongoing myocardial infarctions, require that the fastest path to recanalization of the vessel be selected. On average, a femoral approach saves only a few minutes but this may already be significant during acute myocardial infarction. Moreover, immediate mobilization is not an issue in that setting. While it is possible that the expected advantage of a femoral approach under these circumstances is forfeited by clinically relevant or even fatal access site bleeding, this is avoidable by puncturing distal to the inguinal skin crease, thereby precluding the possibility of retroperitoneal haemorrhage, and, perhaps, by using small catheters and closure devices. An operator inexperienced with the radial approach feeling compelled to use it in the middle of night in a patient with acute myocardial infarction because of the survival benefit (in literature that may at best be valid for radial aficionados) is a detrimental scenario for the patient.

Closure of the patent foramen ovale

The potential of a net benefit by closing the patent foramen ovale (PFO) is likely to be underestimated because of imperfect designs of the respective randomized trials.[32,33] As explained with the parachute example above, the assessment of the results was conducted before the point in time when it can be assumed that the majority of potentially preventable events will have happened. In contrast to the parachute example, this is not minutes but rather decades with regard to the PFO closure. A comparative study with random allocation of patients to PFO closure or medical treatment with at least one decade of follow-up did indeed show a mortality benefit (yearly mortality rate of 0.4% with PFO closure and 1.1% without, $P = 0.03$).[34] Likewise, the randomized evaluation of recurrent stroke comparing PFO closure to establish current standard of care treatment trial (RESPECT)[33] showed a significant reduction of stroke even according to the intention-to-treat principle when comparing PFO closure with treatment with antiplatelet agents only. This still leaves the option of life-long treatment with oral anticoagulation as a valid alternative to PFO closure at least when looking only at data of a follow-up of a couple of years. However, an outpatient procedure lasting <30 min, requiring no physical restrictions whatsoever thereafter, and producing practically no

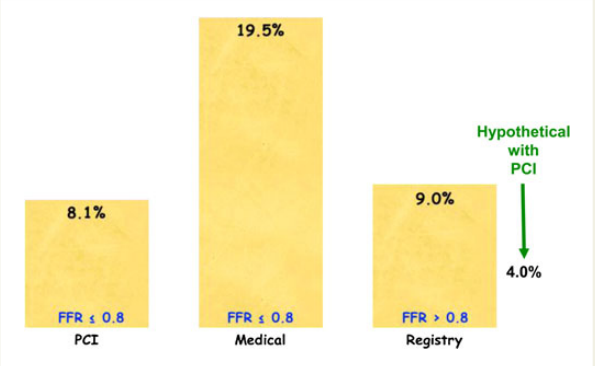

Figure 5 Clinical outcome of the three groups examined in the fractional flow reserve vs. angiography for guidance of percutaneous coronary intervention in patients with multivessel coronary artery disease (FAME) II trial.[19] The trial randomized 1220 patients to percutaneous coronary intervention with a drug-eluting stent or to conservative treatment (Medical) if their fractional flow reserve was ≤0.8 or followed them in a registry if the fractional flow reserve was >0.8. The authors concluded that an abnormal (FFR ≤ 0.8) had identified patients needing percutaneous coronary intervention as the recurrence of symptoms prompting an intervention was significantly higher in the conservative group (middle panel) than in the percutaneous coronary intervention group (left panel). This appears trivial considering that the patients presented for a treatment of their symptoms. Those who did not get to treatment must be more likely to rebounce asking for the treatment than those who did get to treatment upfront. What appears rather strange is that the authors pointed to the efficacy of the treatment also by using the fact that the registry patients (those with a normal FFR > 0.8) had an almost identical event rate (right panel) to that of the patients with a pathological FFR ≤ 0.8 and percutaneous coronary intervention. It has to come to mind here that if the registry patients also had undergone percutaneous coronary intervention, their event rate most probably would have been similarly reduced as the event rate was reduced in the treated patients with a pathological FFR ≤ 0.8. So hypothetically a chance was missed to free at least half of the patients with a normal FFR > 0.8 from further events (right arrow), which mostly was a need for percutaneous coronary intervention during follow-up.

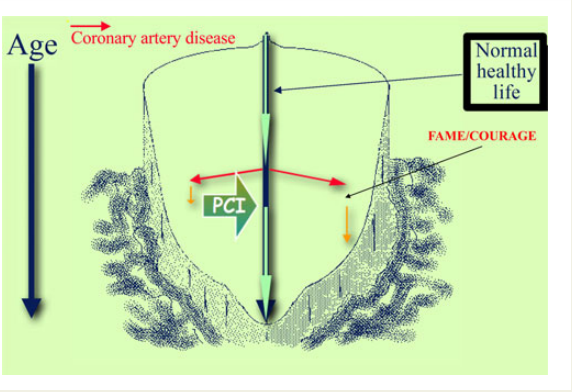

Figure 6 Methaphorical depiction of coronary artery disease. Life can be pictured as a steady forward motion on a high plane that is narrow at the very beginning (newborn phase), rather broad throughout young and middle age, but then gets narrower again with increasing age. Deviating from the safe centre line occurs with any kind of disease, in particular with coronary artery disease. Although a coronary stenosis may be stabilized and the patient does not necessarily feel the deviation from the safe centre line, it appears reasonable to perform a percutaneous coronary intervention to continue life again on the centre line, at least until a new lesion pops up. The fractional flow reserve vs. angiography for guidance of percutaneous coronary intervention in patients with multivessel coronary artery disease (FAME)[19,21] and also the clinical outcomes utilizing revascularization and aggressive drug evaluation (COURAGE)[22] trials insinuate that it is justified not to perform percutaneous coronary intervention by just assessing whether the patients are alive and stable during a limited follow-up. The diagram clearly suggests that the long-term course appears more favourable in the example on the left side of the panel, i.e. with percutaneous coronary intervention, even if there is no further progression of disease which would render the already unfavourable proximity to the dangerous precipice even more precarious.

complications appears a much better deal than life-long oral anticoagulation with an ever accruing bleeding rate, not to mention the cost and nuisance of drug intake. While the number needed to treat to prevent one stroke with PFO closure appears high with ~200 at 1 year, it is only 2 at 50 years,[32,33] a life expectation not uncommon when the question of PFO closure arises.

Transarterial aortic valve implantation

The advent of transarterial aortic valve implantation (TAVI) also currently falls short of full clinical exploitation as a consequence of adherence to evidence-based medicine in a way that is unfavourable to the patients. It is accepted that TAVI provides a mortality benefit over medical treatment in inoperable[35] or over surgical treatment in high-risk patients.[36] This was confirmed also in the CoreValve US clinical trial randomizing variable risk patients to either TAVI or surgical valve replacement[37] and showing that mortality in high-risk patients was significantly lower with TAVI at 22% compared with 29% with surgical valve replacement ($P = 0.04$). Moreover, the aortic valve area remained larger with TAVI up to 2 years and the transaortic pressure gradient lower. The longevity of at least the two market leading TAVI valve types can be assumed competitive with that of surgically implanted valves after observing thousands of them for at least 5 years and seeing no trend of premature valve degradation with TAVI compared with surgery. Having digested all this, it appears counterproductive to present patients to a heart team to decide whether they undergo TAVI or surgical valve replacement. Obviously, the surgeons in the heart team will point to the lack of randomized data in low-risk surgical patients and claim them for open heart surgery. This is not in the interest of the patients. It is safely deducible that a procedure like TAVI that proved equally successful to and less risky and painful than open heart surgery in difficult patients will also be feasible in facile patients. It can also be anticipated that the banes of TAVI such as paravalvular leaks or ruptures, ostial coronary obstruction, need for pacemaker implantation, and access problems in the peripheral vessels will be less common in the younger and healthier

patients. In a way, it is like having tested a pair of hiking boots by conquering Mount Everest several times. It appears as ridiculous to demand that before using these boots for climbing a hill, they should again be thoroughly tested under these new circumstances. While it is always commendable to consult with colleagues on a particular patient, straightforward coronary situations and TAVI in otherwise healthy persons do not need and are unlikely to benefit from such a preoperative team discussion.

Conclusion

It is laudable that physicians, healthcare providers, drug producers, and device manufacturers follow the request of authorities and ethical committees to painstakingly test every new diagnostic or therapeutic approach in a randomized fashion and only introduce them into the routine clinical management if they prove significantly better than what was available previously. However, there are more than a few situations where advantages are proved but not really there or, vice versa, where waiting for the results of randomized trials may preclude patients from an apparently good thing while the trials are ongoing. In particular, preventive procedures such as the closure of the PFO need studies with >10 years of follow-up to be able to prove the expected benefit. Should all patients outside such a trial be deprived of a potentially life-saving simple intervention? Certainly not. Let us assume somebody develops a vaccination against Alzheimer's disease that is extremely likely to be effective and have little side effects. According to modern evidence-based medicine and publication rigour nobody should be vaccinated until a correctly conducted randomized trial has been led to the projected final endpoint (40-year follow-up in that case) and published in a reputable journal. Imagine the missed chances when reading that paper in 2056 and thinking 'I expected these excellent results of the vaccination all along'.

Even if we are determined to perfectly juggle evidence-based medicine, experience, and common sense with the patient's best interests in mind, our hands may be tied by a remuneration process immune to common sense and lagging behind for what appears to be eternities.[38]

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